Prehospital Pain Medication Use by U.S. Forces in Afghanistan

Col Stacy A. Shackelford, USAF MC; Marcie Fowler, PhD†; Capt Keith Schultz, USAF NC‡; CPT Angela Summers, NC USA§; Lt Col Samuel M. Galvagno, USAFR MC, SFS‖; COL Kirby R. Gross, MC USA†; LTC Robert L. Mabry, MC USA†; Col Jeffrey A. Bailey, USAF MC†; COL Russ S. Kotwal, MC USA†; CAPT Frank K. Butler, MC USN (Ret.)†*

ABSTRACT We report the results of a process improvement initiative to examine the current use and safety of prehospital pain medications by U.S. Forces in Afghanistan. Prehospital pain medication data were prospectively collected on 309 casualties evacuated from point of injury (POI) to surgical hospitals from October 2012 to March 2013. Vital signs obtained from POI and flight medics and on arrival to surgical hospitals were compared using one-way analysis of variance test. 119 casualties (39%) received pain medication during POI care and 283 (92%) received pain medication during tactical evacuation (TACEVAC). Morphine and oral transmucosal fentanyl citrate were the most commonly used pain medications during POI care, whereas ketamine and fentanyl predominated during TACEVAC. Ketamine was associated with increase in systolic blood pressure compared to morphine ($+7 \pm 17$ versus -3 ± 14 mm Hg, $p = 0.04$). There was no difference in vital signs on arrival to the hospital between casualties who received no pain medication, morphine, fentanyl, or ketamine during TACEVAC. In this convenience sample, fentanyl and ketamine were as safe as morphine for prehospital use within the dose ranges administered. Future efforts to improve battlefield pain control should focus on improved delivery of pain control at POI and the role of combination therapies.

INTRODUCTION

Pain control for battle injuries has been recognized as essential since the U.S. Civil War when morphine was first introduced on the battlefield.[1] Administered with the primary goal of alleviating suffering, the early use of opioid pain medications has accompanied progressive advancements in prehospital care. Evidence has also linked early use of pain medication after injury to a reduced risk of post-traumatic stress disorder for civilian trauma victims as well as combat casualties.[2–5] Although morphine has remained the foundation of battlefield pain control for more than a century, additional medications have been gradually introduced over the past decade. Recent conflicts have witnessed the introduction of fentanyl, including oral transmucosal fentanyl citrate (OTFC), as well as ketamine for prehospital use.[6,7]

Although intramuscular (IM) morphine has long been the battlefield analgesic of choice for the U.S. military, its safety and efficacy have not been well documented. As early as World War II, physicians reported a number of deaths because of the delayed effects of morphine given IM or subcutaneously to cold and hypovolemic battle casualties.[8] Intravenous (IV) morphine was recommended as an alternative in the original Tactical Combat Casualty Care (TCCC) article, both to increase the speed of pain relief and to decrease the chance of overdose.[9] TCCC guidelines were updated to include the options of OTFC in 2006[6,10,11] and ketamine in 2012[7] as alternatives to morphine for prehospital use. In 2014, the guidelines were further updated to recommend OTFC as first-line pain medication for casualties without risk of shock or respiratory depression and ketamine for casualties with such risk. Parenteral morphine was recommended only as an alternative.[12]

Risks of opioid pain medications are primarily related to dose-related respiratory depression and hypotension. Additionally, both opioids and ketamine can alter the casualties' neurologic status, further limiting neurologic assessment as well as combat effectiveness, and in the case of ketamine, agitated emergence reactions may occur.[13]

We undertook a process improvement initiative to evaluate current use of prehospital pain medications by U.S. Forces in Afghanistan and to compare vital sign changes after administration of pain medications in the prehospital environment.

METHODS

Following determination by the Joint Casualty Care Research Team that this initiative met criteria to be performed as a process improvement project (e.g., unblinded, bias may be present but consistent, sample size just adequate, hypothesis flexible, and data to be used only by those involved in the improvement), prehospital pain medication data were prospectively collected under a process improvement monitoring protocol on a convenience sample of 309 casualties evacuated from point of injury (POI) to a Role 2 or 3 surgical hospital from October 2012 to March 2013. Prehospital pain

*Center for the Sustainment of Trauma and Readiness Skills, R Adams Cowley Shock Trauma Center, University of Maryland Medical Center, 22 South Greene Street, Baltimore, MD 21201.

†Joint Trauma System, US Army Institute of Surgical Research, 3698 Chambers Pass, Fort Sam Houston, TX 78234.

‡81 Medical Operations Squadron, Keesler AFB, MS 39534.

§212 Combat Support Hospital, Miesau AD, Germany.

‖Department of Anesthesiology, University of Maryland Medical Center, 22 South Greene Street, Baltimore, MD 21201.

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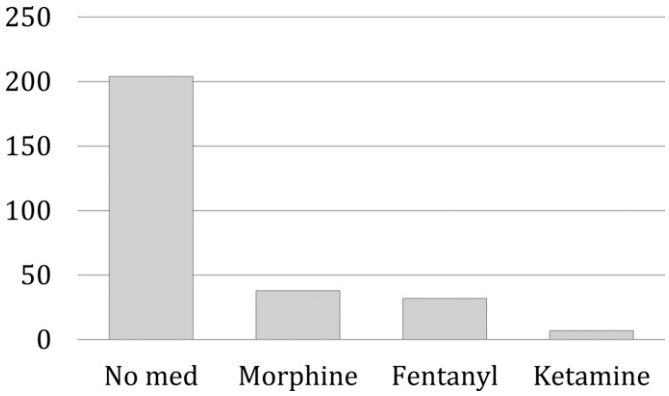

FIGURE 1. Pain medications given during POI care.

medications were given in accordance with unit standard operating protocols and TCCC guidelines dated June 25, 2012.[14] All available prehospital documentation was reviewed. Medications and vital signs during POI care before tactical evacuation (TACEVAC) were documented on TCCC cards (DA Form 7656) or on standard evacuation patient care reports when reported by ground to flight medics. Medications and vital signs during TACEVAC were recorded on standard evacuation patient care reports. During TACEVAC, the first and last sets of vital signs were recorded and changes in vital signs were calculated. All medic-reported reactions were recorded.

Ten of 309 (3.2%) casualties during POI care and 8 of 309 (2.6%) casualties during TACEVAC care received a second pain or sedation medication. For the purpose of analysis, these patients were grouped with the first pain medication received.

Comparison of vital signs for each pain medication received (morphine, fentanyl, ketamine, or none) was performed with a one-way analysis of variance. Data were analyzed using the Statistical Analytical Software (SAS 9.2; SAS Institute, Cary, North Carolina). Categorical data were summarized using percentages and frequencies. Continuous variables were tested for normality. For those that meet the criteria for normality, means and standard deviations (SDs) were used as summary statistics and analyzed using Student's *t*-test and analysis of variance with a Tukey adjustment for pairwise comparisons. Non-normally distributed variables were analyzed using Kruskal–Wallis test with a Steel–Dwass adjustment for pairwise comparisons, and medians with interquartile ranges (IQRs) were used for summary statistics. Significance for results used a two-sided test and was established when *p*-values were less than 0.05.

RESULTS

The most common mechanism of injury in this cohort of 309 casualties was blast injury, which occurred in 175 (56%), followed by gunshot wound in 99 (32%), motor vehicle crash in 14 (4.5%), nonbattle injury in 7 (2.2%), and other mechanism in 14 (4.5%).

The dominant injury types included multiple fragment wounds in 64 (21%), extremity gunshot wound in 58 (19%), major amputation of one or more extremities in 48 (16%), extremity fracture in 42 (14%), penetrating torso trauma in 41 (13%), head/neck injury in 39 (13%), suspected spine injury in 9 (2.9%), and other in 8 (2.6%).

119 casualties (39%) received a pain medication during POI care and 283 (92%) received a pain medication during TACEVAC. Medications received during POI care are illustrated in Figure 1. There was no difference in systolic blood pressure (SBP), respiratory rate (RR), heart rate (HR), or oxygen saturation (SaO_2) for the 4 groups who received no pain medication, morphine, fentanyl, or ketamine among patients with POI phase vital signs available ($n = 99$, $p > 0.05$ for all pairs) (Table I).

Medications received during TACEVAC care are illustrated in Figure 2. During TACEVAC, casualties who received ketamine had a significantly lower SBP before receiving pain medication than casualties who received morphine ($p = 0.03$). The change in SBP before and after receiving pain medication was also significantly different ($p = 0.04$) between morphine (decreased by 3 ± 14 mm Hg) and ketamine (increased by 7 ± 17 mm Hg). There was no change in SBP for casualties receiving fentanyl (0 ± 14 mm Hg).

RR increased significantly ($p < 0.05$) by an average of 4 ± 12 breaths per minute for casualties who received no pain medication during TACEVAC. Among those who did receive pain medication, there was no difference in RR between the 3 medications (Table II).

Casualties who did not receive pain medication during TACEVAC had a significantly lower ($p < 0.0001$) starting pain score compared to those who did receive pain medication: no medication = 3 (1–4) (median [IQR]), morphine = 7 (5–8), fentanyl = 6 (5–8), and ketamine = 7 (5–8). The decrease in

TABLE I. POI Vital Signs for Casualties Receiving the Designated Medications ($p > 0.05$ for All Pairs)

Vital Sign	No Medication	Morphine	Fentanyl	Ketamine	*N* (Data Available)
SBP, mm Hg (Mean ± SD)	108 ± 20	105 ± 23	114 ± 28	108 ± 27	89
HR, bpm (Mean ± SD)	99 ± 26	89 ± 17	95 ± 23	89 ± 19	95
RR, bpm (Mean ± SD)	18 ± 5	20 ± 6	19 ± 5	20 ± 8	79
SaO_2, % (Mean ± SD)	96 ± 5	97 ± 1	99 ± 1	95 ± 5	37
GCS (Mean ± SD)	14.4 ± 1.3	14.3 ± 1.1	14.3 ± 1.8	13.2 ± 2.9	128
Pain score 1–10 (Median, IQR)	6 (5 to 7)	5.5 (3 to 7)	5 (4 to 7)	5 (3 to 6.5)	44

GCS, Glasgow Coma Scale.

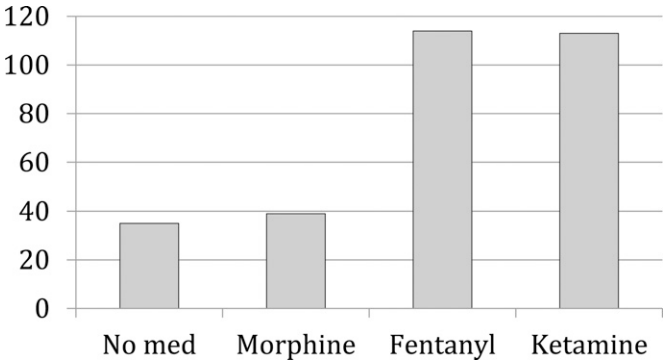

FIGURE 2. Pain medications given during TACEVAC.

pain scores during TACEVAC was not significantly different for any of the three pain medications received ($p > 0.05$).

Hospital arrival vital signs were available only for casualties transported to U.S. or U.K. hospitals ($n = 138$). There was no difference in arrival vital signs for any pain medication received or no medication (Table III).

The mean ± SD dose, route, and dose ranges of all pain medications given during POI and TACEVAC care are shown in Table IV.

Combinations of pain medications received by casualties during POI and TACEVAC care are illustrated in Figure 3. Of note, all casualties received pain medication during at least one of the phases of care, and there were no casualties who did not receive any pain medication. Although the majority of casualties received a single agent, 69 (22%) received a combination of medications. The most common combinations received were morphine + ketamine ($n = 20$), fentanyl + ketamine ($n = 18$), and morphine + fentanyl ($n = 20$). Thirty-two percent ($n = 37$) of casualties who received ketamine during TACEVAC also received an opioid (morphine or fentanyl) during POI care. Other pain and sedating medications were received by 17 (5.5%) casualties (7 [2.2%] during POI and 10 [3.2%] during TACEVAC) to include ketorolac, midazolam, diazepam, and acetaminophen.

DISCUSSION

The evolution of pain control on the battlefield has progressed slowly from morphine injection, a method that prevailed for over a century from the time it was introduced during the Civil War until well into the wars in Iraq and Afghanistan.[1] Although survival from battle injuries has increased through the use of improved battlefield hemorrhage control,[10,15] improved resuscitation,[16] increased blood product availability,[17] forward surgery, and rapid evacuation to higher levels of care,[18,19] improvements in early management of pain on the battlefield have evolved more slowly. Historically, morphine has been administered on the battlefield by autoinjectors capable of delivering 10 mg IM to relieve severe pain[20]; however, this route of administration is limited by variable rates of absorption and the potential for delayed adverse reaction.[8,9] IV morphine injection provides more rapid pain relief. Both IM and IV morphine may be associated with respiratory depression and hypotension, but the likelihood of this occurring may be increased when morphine is administered IM because of multiple doses being given as a result of the delayed onset of action.[8,9]

TABLE II. TACEVAC Initial Vital Signs and Change in Vital Signs During TACEVAC for Casualties Receiving the Designated Medications

Vital Sign	No Medication	Morphine	Fentanyl	Ketamine	*N* (Data Available)
Pre-med SBP	122 ± 24	127 ± 18*	121 ± 21	115 ± 25*	291
Change in SBP	+2 ± 23	−3 ± 13*	0 ± 14	+7 ± 17*	213
Pre-med HR	94 ± 24	95 ± 21	96 ± 24	102 ± 26	296
Change in HR	+3 ± 13	−3 ± 23	−3 ± 14	−5 ± 20	222
Pre-med RR	16 ± 4	18 ± 5	17 ± 8	17 ± 4	278
Change in RR	+4 ± 12*	−1 ± 2	−1 ± 2	−1 ± 4	197
Pre-med SaO_2	98 ± 2	98 ± 2	98 ± 4	96 ± 4	280
Change in SaO_2	+2 ± 3	+4 ± 2	+1 ± 2	+2 ± 4	211
Initial Pain Score 1–10 (Median, IQR)	3 (1 to 4)*	7 (5 to 8)	6 (5 to 8)	7 (5 to 8)	221
Change in Pain Score (Median, IQR)	0 (0-0)*	−3 (−5 to −1)	−3 (−4 to −2)	−4 (−6 to −2)	144

*$p < 0.05$.

TABLE III. Trauma Bay Arrival Vital Signs for Casualties Who Received the Designated Medications During TACEVAC ($p > 0.05$ for All Pairs)

Vital Sign	No Medication	Morphine	Fentanyl	Ketamine	*N* (Data Available)
Arrival SBP	136 ± 21	136 ± 21	132 ± 23	132 ± 25	136
Arrival HR	94 ± 25	92 ± 28	92 ± 25	99 ± 27	138
Arrival RR	20 ± 5	22 ± 16	20 ± 10	21 ± 8	129
Arrival SaO_2	98 ± 2	98 ± 2	98 ± 3	99 ± 1	138
Arrival Pain Score 1–10 (median, IQR)	5 (1 to 9)	4 (1 to 7)	5 (1 to 10)	3 (0 to 9)	74

TABLE IV. Mean ± SD and Dose Range of Pain Medications Received During POI and TACEVAC Care

	POI			TACEVAC		
Pain and Sedation Medication	Dose (Mean ± SD)	Dose Range	No. of Casualties	Dose (Mean ± SD)	Dose Range	No. of Casualties
Morphine IV (mg)	8.3 ± 2.8	2–10	30	6.9 ± 2.8	1–10	35
Morphine IM (mg)	9.4 ± 2.5	2–12	24	7.9 ± 3.2	2.5–10	5
Fentanyl IV (mcg)	121 ± 49	50–200	7	77 ± 38	25–200	87
Fentanyl IM (mcg)	—	—	0	75 ± 35	25–100	5
Fentanyl OTFC (mcg)	800 ± 0	800	33	800 ± 0	800	25
Ketamine IV (mg)	57 ± 45	10–125	9	43 ± 25	10–150	81
Ketamine IM (mg)	77 ± 79	10–150	6	58 ± 26	20–100	35
Midazolam IV (mg)	3.3 ± 2.1	1–5	4	3.0 ± 1.4	1–5	7
Diazepam IV (mg)	15 ± 14	5–25	2	25 ± 0	25	2
Ketoralac (mg)	23 ± 12	10–30	3	30 ± 0	30	1
Acetaminophen (mg)	500	500	1	—	—	0

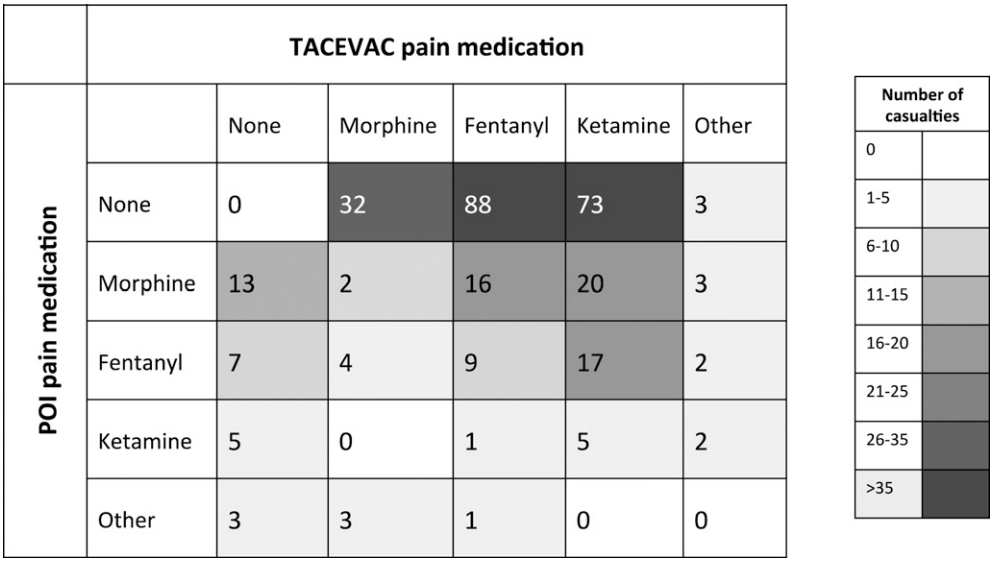

FIGURE 3. Combinations of pain medications received by casualties during POI and TACEVAC care.

The placement of an IV catheter is often time consuming and may be impossible in tactical environments. This fact was a major consideration in the incorporation of OTFC or "fentanyl lollipops" as a TCCC-recommended analgesic option in 2006. OTFC safety was further improved using medic-recommended techniques for dislodging the lozenge from an oversedated casualty such as taping the lozenge to a casualty's finger or using a safety pin and rubber band to attach the lozenge (under tension) to the casualty's uniform or plate carrier,[12] thereby causing the lozenge to be pulled from the mouth if the casualty drifts into unconsciousness. The use of OTFC has been shown to be safe and effective on the battlefield, although it was accompanied by nausea in 13% of the reported cases. Because it is an opioid, fentanyl also has the potential for adverse effects to include respiratory suppression, hypotension, and bradycardia.[6,21]

The addition of ketamine as an option for battlefield analgesia was recommended by the Defense Health Board in 2012[7] after strong endorsement by the Committee on TCCC and the Trauma and Injury Subcommittee of the Defense Health Board. Although Food and Drug Administration-approved as a dissociative anesthetic agent, ketamine is also an effective analgesic at lower doses, either alone or in combination with narcotics and can be administered through multiple routes.[22] Pharmacologic properties of ketamine include the desirable effects of rapid (within 5 minutes) onset of action when administered IM, minimal respiratory suppression, mild increase in HR and blood pressure, and reduced nausea and vomiting compared to narcotics; however, ketamine has also been associated with dysphoria and stimulation of secretions when given at higher anesthetic doses.[13,23–25] In recent years, low-dose ketamine has been increasingly used in far-forward environments and is currently the first-line pain medication for casualties in shock or at risk of shock according to TCCC guidelines. Earlier concerns for elevation in intracerebral or intraocular pressure have been re-examined in the light of new evidence and are no longer considered contraindications to the use of ketamine for pain control on the battlefield,

especially when ketamine is chosen for the specific intent of avoiding cardiorespiratory depression in casualties who are in shock or in respiratory distress.[12,26] Intranasal ketamine was approved as an alternative method of delivery without injection; however, during the time of the current project, this medication required pharmacy compounding and was not available for prehospital use.

In this process improvement initiative, we sought to describe the current use of pain medication on the battlefield, including doses, routes, and combinations of medications received. We found that 100% of the casualties in our sample received a pain medication before arrival at the hospital, either during POI or TACEVAC care. However, only 39% of casualties received a pain medication during POI care. Although physicians have previously been shown to have the capability to provide good analgesic care at Role 1 facilities, analgesia training efforts are required for all providers throughout the entire continuum of prehospital, forward-deployed, and en route care.[27] Our study provides preliminary support for the safety of prehospital analgesic administration. There were no adverse reactions recorded for any of the pain medications used, with all of the doses falling within a low to moderate dose for each agent. The combination of an opioid and ketamine may provide improved pain control, a strategy that warrants further investigation. Although the majority of patients in this review received a single agent for pain control before reaching the hospital, 38 (12%) received an opioid during POI care before receiving ketamine during TACEVAC care.

We found that casualties who received ketamine during TACEVAC had a significantly lower blood pressure before receiving pain medication; this is underscored by the TCCC and unit guidelines that encourage the use of ketamine for casualties in shock or at risk of shock. During TACEVAC, ketamine was also found to significantly raise the blood pressure in comparison to morphine, with approximately 10 mm Hg difference in postmedication blood pressure between casualties receiving morphine and those receiving ketamine, further buttressing the current guidelines for the use of ketamine as the first choice of pain medication for casualties in shock. Ketamine may not only provide improved hemodynamics, but in at least one recent randomized study, when combined with midazolam, hypoxemia and duration of hypoxia were significantly lower when compared to a combination regimen with midazolam–fentanyl.[28]

We also evaluated the response to pain medications through vital signs recorded before and after receiving pain medication, looking for the major adverse effects of respiratory suppression and hypotension. In this sample, there was no decrease in RR or SaO_2 for the three pain medications commonly used (morphine, fentanyl, and ketamine) within the dose ranges used. Further review of individual patient records did not reveal a single episode of respiratory depression that was attributed to pain medications, although airway interventions were not uncommon in this cohort of patients. Eighteen casualties (5.8%) were intubated in the prehospital arena, and oxygen was routinely administered by face mask during TACEVAC. There was no difference in arrival RR or SaO_2 for patients delivered to U.S. and U.K. hospitals (the postarrival status of patients delivered to local Afghan hospitals was not obtained).

Morphine was associated with a slight decrease in SBP (mean decrease of 3 ± 13 mm Hg), whereas fentanyl was not associated with a change in SBP (0 ± 14 mm Hg), and ketamine was associated with a slight increase in SBP (7 ± 17 mm Hg) during TACEVAC. On arrival to the hospital, there was no difference in SBP or HR between casualties who did not receive pain medication during TACEVAC and any of the three commonly used pain medications received during TACEVAC, in spite of the lower initial SBP for casualties who received ketamine.

Pain scores were also assessed during TACEVAC when available. There was no significant difference in pain scores or change in pain score for any of the pain medications received during TACEVAC, although those casualties who received no pain medication had no change in pain score as expected. Median pain scores decreased by 3 to 4 during TACEVAC for each of the three medications received. By comparison, previous studies showed that casualties receiving OTFC reported a mean decrease in pain scores of 5.77 during the first minutes after administration at POI with a standard dose of 1600 μcg[6] and a mean decrease of 4.8 with doses averaging 962 μcg.[21]

Our review shows that morphine is still the most commonly used pain medication during POI care. This is largely because of the fact that morphine autoinjectors are the most commonly fielded battlefield analgesic, rather than a reflection of demonstrated superiority to the other options.[12,29] However, the use of OTFC and ketamine was not uncommon. It is likely that pain medication administered at the POI was underreported in this series because of challenges with data collection. Improved efforts in battlefield documentation will likely yield a clearer description in the future.[30]

During TACEVAC, the use of both fentanyl and ketamine by flight medics has largely supplanted the use of morphine. In this sample, the use of these newer agents was found to be at least as safe and effective as morphine for prehospital pain control in terms of the complications of respiratory suppression, hypotension, and pain scores. In the future, multimodal therapy may encompass a wider range of procedures and injuries with the aim of providing a more comprehensive and aggressive pain management strategy with implications for the civilian arena as well.[31]

The data collected were limited by incomplete documentation during POI care, uncertainty of exact times for pain medication received and postmedication vital signs during TACEVAC, and a complete lack of hospital arrival data for patients delivered to local Afghan hospitals. Nevertheless, it remains the most complete description to date of modern prehospital pain control during wartime.

CONCLUSION

In this convenience sample, fentanyl and ketamine were as safe as morphine for prehospital use within the dose ranges administered. Although this process improvement project cannot be considered definitive evidence, the results do support current TCCC recommendations to use ketamine (either IV or IM) or OTFC as the prehospital main medications of choice, and these medications were at least as safe as the previous standard of care using morphine. Future consideration should be given to adding IV fentanyl to the TCCC guidelines as an option during TACEVAC care. Casualties who received ketamine had a lower starting SBP, and SBP increased after treatment, supporting current guidelines to use ketamine as the first-line pain medication for casualties in shock or at risk of shock. Future efforts to improve battlefield pain control should focus on improved delivery of pain control at the POI and the role and safety of combination therapy with ketamine and fentanyl. Investigation of improved methods of delivery, such as ketamine autoinjectors or preformulated intranasal ketamine, may contribute to improved pain medication delivery at the POI.

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